REMARKS/ARGUMENTS

The Status of the Claims.

Claims 34 to 55 and 62 to 67 are pending with entry of this amendment, claims 1 to 33 and 56 to 61 being cancelled. Claims 34 and 41 are amended herein. Claims 62 to 67 are newly added. These amendments introduce no new matter and support is replete throughout the specification. These amendments are made without prejudice and are not to be construed as abandonment of the previously claimed subject matter or agreement with any objection or rejection of record.

With respect to claim 34, support for conservative variations to SEQ ID NO: 2 can be found throughout the original specification. For example, see paragraphs 12, 29, 34, 46, 67, and the section entitled "Conservative Variations" starting at paragraph 92.

With respect to claim 41, the amendment merely further clarifies the identified plasmid, as requested by the Office. In addition, the amendment deletes an objected term.

With respect to claims 62 to 64, support for 90%, 95% and 98% identity to SEQ ID NO: 2 and proline 144 can be found throughout the specification. For example, see specification at paragraphs 12, 21, 29, 30, 65, 132 and 168.

With regard to new claim 65, support for further screening can be found throughout the specification. For example, see paragraph 183, and the section entitled "Screening O-RS constructs" starting at paragraph 133.

With regard to new claim 66, support can be found, e.g., at paragraph 179.

With regard to new claim 67, support can be found, e.g., at paragraph 183.

Applicants submit that no new matter has been added to the application by way of the above Amendment. Accordingly, entry of the Amendment is respectfully requested.

Interview Summary.

A telephonic Interview was held on October 9, 2008, with Examiner Leavitt, SPE Woitach and Applicant's Representative, Gary Baker, discussing independent claim 34.

There was agreement that claims including, e.g., 100% sequence identity to past-tense working examples are enabled. Applicant's Representative noted structure/function relationships have been provided, almost residue by residue, through the exemplary O-tRNA sequence. Applicant's representative noted that the general structure of the O-RS is presented and known, including certain modifications predicted and shown to provide the particular function. Supervisor Woitach noted that this type of information can be used to justify a finding of enablement for claimed embodiments beyond the past-tense working examples.

The Information Disclosure Statement.

The Office has not considered certain references from the Information Disclosure Statements (Form 1449) submitted on October 4, 2006 and December 31, 2007. Enclosed are Applicant's best copies available for the objected references. Applicants note that the John Wiley and Sons reference (#1 of 12/21/07 IDS)is an excerpt from a Biochemistry text and the cited part is provided. The Science reference (#2 of the 12/21/07 IDS) is the complete reference and believed to be the full text. Applicants request consideration of these legible and complete as offered references.

Claim Objections.

Claims 35 and 41 were objected for alleged lack of clarity.

With regard to the claim 35, the objected term has been deleted. Therefore, Applicants request withdrawal of the objection to the claim.

With regard to claim 41, pVal144ProBsTrpRS is the non-abbreviated name of a disclosed plasmid. However, the claim has been amended to further clarify the precise nature of the cited plasmid without actually changing the scope of the claimed subject matter.

Because the claim objections have been addressed, Applicants respectfully request withdrawal of the objections to claims 35 and 41.

35 U.S.C. §112, Second Paragraph.

Claim 41 was rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite because of the term "substantially". Because the term is deleted from the present claim 41, Applicants request withdrawal of the rejection.

35 U.S.C. §112, First Paragraph.

Claims 34 to 55 were rejected under 35 U.S.C. §112, first paragraph, for alleged lack of enablement. To the extent the rejection is deemed applicable to the amended claims, Applicants traverse.

To be an enabling disclosure under § 112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. That some experimentation is necessary does not constitute a lack of enablement; the amount of experimentation, however, must not be unduly extensive. *See* In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *See id.*

The Action of August 4, 2008, acknowledges enablement for: a method of incorporating 5-substituted tryptophan unnatural amino acid into a peptide, the method comprising, preparing a construct comprising a nucleic acid sequence consisting of SEQ ID NO: 1 encoding the orthogonal mutant tryptophanyl-tRNA synthetase (O-muTrpRS) of SEQ ID NO: 2, preparing a construct comprising a nucleic acid construct consisting of SEQ ID NO: 3 encoding an orthogonal tRNA (O-tRNA), and introducing the O-muTrpRS construct and the O-tRNA construct into a mammalian cell to preferentially aminoacylate an expressed O-tRNA with the 5-substituted tryptophan unnatural amino acid, wherein the aminoacylation is catalyzed by an expressed O-muTrpRS. The Office acknowledges essentially a past tense working example provided in the original specification, without acknowledging one of skill can practice anything broader without undue experimentation. Such a stand is unreasonable, in light of the controlling *Wands* case where the Court found enablement of generic claims to monoclonal antibodies to an antigen where no structural information for the antibody was provided and experimentation routinely lead to a failure rate of 98% or higher. Here, Applicants have provided abundant structural information regarding all elements of the

claims and guidance allowing a high degree of success in conservative substitutions of these components. Moreover, even without the benefit of the provided structure/functional information, the specification provides functional structures and powerful positive and negative selection techniques that have been shown to readily identify functional variants even from randomly mutated libraries.

Although Applicants believe the original claims are enabled, in order to expedite prosecution of the claims, they have been amended, e.g., to include certain structures found to enhance function.

The Examiner notes at page 7 of the Action that "[s]ince the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge of an[d] guidance with regards to which amino acids in the protein's sequence if any, are tolerant of modification and which are conserved ... and detailed knowledge of the ways in which the proteins' structure relates to function." Here, the skill in the art and guidance of the present specification provide abundant information on what peptide or nucleic acid residues of system components can be conservatively substituted with a reasonable probability of retaining a useful degree of functionality. Applicants believe the original specification provides exhaustive structural information to guide one of skill in logical and predictable conservative sequence substitutions. However, such enablement aside, the statement of the Office above is not on point because Applicants have provided functional starting structures and screening methods that one of skill can undeniably use to readily obtain functional variants, even if the specification lacked a discussion of structure-function relationships (which is does not lack), to enable routine production of logically or systematically produced functional variants.

The rejection must be withdrawn because 1) one of skill can rationally select variants with a high degree of predictability that function adequately in the claimed methods, and 2) one of skill can start with the given sequences and use the given screening techniques to readily obtain functional conservative variants for use in the claimed methods.

The quantity of experimentation necessary to practice the claimed invention is the first *Wands* factor for evaluation of enablement. Even where some of the conservative

variants generated by one of skill have reduced function, the *Wands* Court has found this to be quite acceptable. The Court first noted that the experimental process for making antibodies that bind the relevant antigen were set forth in the application. In essence, this process included an elaborate hybridoma fusion screening and manipulation procedure, followed by a binding screen to identify "high binders" followed by another screening procedure to identify what type of antibody had been generated (IgM being the desirable antibody type in *Wands*). The PTO argued that less than 3% of hybridomas that were created produced antibodies, and of these, only 20% produced IgM antibodies. The first four hybridoma fusion experiments performed by the Wands inventors were failures, with the next 6 being successful. The Court held that this was not evidence of unpredictability, particularly given that the technique at issue was in general use for antibody production. *Wands* at 1406. Here, on the first try, Applicants have found a working system of the claim without the benefit of hindsight and the teachings they now provide. Given the base structures (not provided at all in *Wands*) one of skill can readily provide additional conservative variant species across the range of the claimed matter.

Here, a working reference sequence is given that will work every time, as compared to the *Wands* screening method known to fail a in substantial portion of attempts. Functional variants can be found easier than in *Wands* because functions of structures in tRNAs and synthetases, including conserved regions, binding pockets and active sites, are known. Indeed, it is likely that more is known about synthetase and tRNA structure than any other biomolecules, due to more than 50 years of intense study of there molecules. For example, the secondary and tertiary structures of thousands of synthetases are known. The folding structures of essentially all of the many thousands of known tRNAs are also known. Further the current specification provides particular structural and functional information, including identification of key structures, such as the Pro144 residue that accommodates 5-substituted analogs in the active site, the location of the binding pocket structures and the α helix structure that positions the Pro144, identified functions of His44 and Asp133, tRNA conserved residues, suggested tRNA modifications, and warnings on residues not to change. See the original specification at starting at paragraph 179 and starting at paragraph 140; and, Figures 1 and 5. This is the kind of information on structure and function the Examiner cites

as supporting broader enablement. A broader acknowledgement of enablement is clearly appropriate in this case.

Even at levels lower than the basic skill in the art, one with basic knowledge in general protein chemistry and genetics could identify functional conservative variations with a predictability well beyond the *Wands* standard. It goes without saying that one of skill could clearly practice the working example, acknowledged as enabled. However, something more must reasonably be considered enabled. For example, one of skill in the art of protein engineering, given the reference sequence and synthetase structural information in the specification and the public domain could surely succeed with minimal experimentation in logical directed conservative substitution of amino acids along the given sequence. For example, avoiding known and identified structural elements, one could easily substitute amino acids conducive to maintenance of scaffolding structures, such as α helices and β sheets, without disrupting secondary and tertiary conformation (Applicants note that controlling law, such as *Wands*, does allow for substantial rates of failure). Even if such substitutions influenced peptide activity, the result would often be a changed activity without total loss of function (see, Office's cited references). In a pioneering reference "Progress toward the evolution of an organism with an expanded genetic code", by Liu, et al., PNAS 96: 4780-4785, at 4782, it is noted that orthogonal components charging 20x less than wild type is sufficient for function. The Office has not provided any citation contradicting the assertions that logically directed substitutions are routine, and that reduced activity still retains useful functionality. References cited by the Office typically express amazement at finding amino acid substitutions in an active site that change activity of a peptide. These results are published in prestigious journals. It is hard to find the relatively rare mutations that destroy functionality, particularly outside of points of external interaction, such as active sites and binding pockets (all of which are known for the synthetases of the invention). One of skill knows that anyone can readily identify functional conservative substitutions that do not change activity of a peptide, and that is why these observations of little interest and are rarely, if ever published.

One of skill in the art could practice the claimed methods, given the starting functional structures, without any consideration of any structure/function relationships,

known or unknown. Using the screening techniques provided in the specification, Applicants were able to provide the specific functioning constructs, without undue experimentation. Applicants provided the structures of the claimed methods starting from non-functional structures. Surely, it can not be considered undue experimentation to accomplish the easier task of starting with functional structures and using the provided mutation and screening techniques to obtain additional functional variants.

In light of the above, experimentation would be minimal, and certainly not "undue" in this art, to successfully practice the present invention, e.g., by logical conservative substitution of any reasonable number amino acids in the reference O-RS, or by random mutation of the given functional structures and screening for related functioning variants.

The amount of guidance presented is substantial, and well beyond that provided in *Wands*. As discussed above, the original specification provides a working reference system, including identification of functional structures one of skill would not substantially modify (see, e.g., paragraphs 140 and 183, materials and methods starting at paragraph 159, and Figures 1 and 5). Alternate resources for system components are identified (see, paragraphs 37, 86, and 88) as are conservative substitutions (see, paragraph 93 and Table 1). Also included are extensive citations of references (e.g., Anderson et al., (2002) *Exploring the Limits of Codon and Anticodon Size*, Chemistry and Biology, 9:237-244; GENBANK; computer-assisted modeling Macromodel version 8.1, Schrodinger, LLC; U.S. Patent Application No. 10/126,927, "In Vivo Incorporation of Unnatural Amino Acids", by Shultz, et al., and U.S. Application No. 10/126,931, "Methods and Compositions for the Production of Orthogonal tRNA - Aminoacyl tRNA Synthetase Pairs" by Shultz, et al.) that would help guide one of skill to identify logical conservative substitutions, within the limitations of the claims, retaining substantial functionality without undue experimentation.

Applicants have noted in the specification that "where a construct has previously been characterized, the construct can be transduced, transformed, or transfected into host cells for expression and production of the O-RS (and/or O-tRNA) of the invention. In many cases a library of alternate candidate constructs is prepared, e.g., for a series of expression, screening, and selection steps to identify the constructs ..." The specification guides one of skill in steps to obtain functional system constituents from non-functional

constituents by, e.g., preparing constructs of foreign RS/tRNA pairs, preparing libraries of mutant constituents, selecting for orthogonal constituents that do not that charge in the endogenous system, screening for suppressing pairs, screening for suppressing pairs that do not charge with natural amino acids, and screening for suppressing pairs that do charge with a 5-substituted tryptophan. Given this guidance and the sequences provided, one of skill can practice the full scope of claimed methods with much less effort, e.g., skipping procedures already completed and screening from libraries with a far higher percentage of functional members. For example, to practice variants of the methods, one of skill would not have to prepare constructs of foreign RS/tRNA pairs, not have to select for orthogonal constituents that do not that charge in the endogenous system, not have to screen for suppressing pairs, and/or not have to screen for suppressing pairs that do not charge with natural amino acids. Because the starting sequences already function, site directed mutant libraries (using structural information provided), or randomly mutated libraries, would necessarily include a far higher population of functional members. The percentage of suppressing pairs that charge with a 5-substituted tryptophan would be orders of magnitude higher. Using the present functioning method and base constituent sequences, and the guidance of the specification, one of skill can practice the claimed methods with a much higher degree of success and predictability than the scientists of *Wands* or the work of the present inventors.

The techniques of positive and negative screening are capable of identifying, e.g., functional orthogonal synthetases charging unnatural amino acids, e.g., from libraries of randomly mutated RSs; wherein the parent RS starts out totally non-functional in the desired orthogonal system. For example, see Liu, *ibid* at 4782, where individual sessions of positive screening provided 130 to 10^5-fold enrichment for functional RSs, and sessions of negative screening provided 4000 to 10^7-fold enrichment for functional RSs. Here, Applicants have provided parent sequences (e.g., RS SEQ ID NO: 2), which already have functional structures. Using the techniques provided, one of skill can easily identify functional mutants based on the identified sequences. Continued rejection requires the Office argue where one of skill in the art can identify a functioning system by mutation of a non-functioning system (as in Lui), it is undue experimentation to identify a functional system from mutants starting with a functional system. This is an objectively unreasonable argument.

The state of the art and the relative skill of those in the art are greater than in *Wands*. *Wands* indicated that the state of the prior art was advanced, with "all of the methods required to practice the invention being known." This is precisely true for the present case as well. Every step used to produce the claimed cells or compositions is known and available, though some, such as the positive-negative screen combine several known methods to achieve the screen. Indeed, given that *Wands* was decided in 1988, it is plain that the state of the prior art is enormously more advanced than it was at the time of the *Wands* decision. The level of skill of practitioners in the field was considered "high" for the *Wands* decision. Obviously, it is much higher now than it was in 1988. The information that biotechnology practitioners are presumed to be aware of has had over 20 years to develop, and the pace of development during that period has been staggering. A typical postdoctoral researcher or principal investigator can, for example, sequence and provide a detailed analysis of an entire genome, or, e.g., hundreds of cloned RS or O-tRNA, in a matter of days or weeks, whereas in 1988, a week could go by to get one simple sequencing reaction to work, due to the extensive manual manipulations that had to be performed. If the level of skill in the art was "high" at the time of *Wands* then it is now positively stratospheric. In any case, any moderately competent molecular biologist, given Applicants' disclosure can certainly perform each and every step required to make the claimed compositions.

A very wide variety of tRNA synthetases were known at the time the invention was filed. For example, Szymanski et al. (2001) "Aminoacyl-tRNA synthetases database" Nucleic Acids Res. 29:288-290 (attached in Appendix A) provides one example database of Aminoacyl-tRNA synthetases. See also: http://rose.man.poznan.pl/aars/index.html. Many synthetases have been described by sequence and are available in the literature—the one web site noted above lists over 1,000 available synthetases, including well over 100 for which the three dimensional crystal structure has been determined. This is one of the most studied and structurally characterized protein families in all of biology. One of skill knew functions of RS structures at the time, so could have practiced functional variants of a given structure without undue experimentation.

The predictability of the art is good, particularly here, where the general structure of a protein is given, including known binding pockets, structural scaffolding, and

active sites. One of skill knows how to make conservative substitutions in less critical areas to retain the secondary and tertiary structures that retain the conformation of active sites with more than a reasonable degree of success. For example, one of skill can have high confidence in substituting one amino acid known to cooperate in α helix stabilization (e.g., alanine) with another amino acid known to cooperate in α helix stabilization (e.g., leucine) with high confidence in retaining functionality of the peptide. This particularly when conserved structures, such as binding pockets and active sites have been identified (as in the present invention). Again, Applicants note that, even without systematic protection of conserved structures, and structures identified as to function, one of skill could predictably screen for functional variants of the provided sequences, even from a randomly mutated library. The predictable success rate would jump astronomically were the mutations logically directed in recognition of functional structures known in the art and provided in the present specification. Enablement does not require absence of failure, or optimum performance of each functional embodiment. In fact, failure was high in *Wands* and many antibodies had sub-optimal affinity for the antigen. Here, failure would be predictably low, and well below the controlling standard set in *Wands*. In fact, it would be unreasonable to argue that functional variants could not be found with reasonable experimentation.

The breadth of the claims is narrow compared to the broad generic claims of the *Wands* antibodies. The current amendments further focus the scope to methods using variants of the provided structures including specific functional structures described in the specification. The present claims are far narrower that the generic monoclonal antibody claims of *Wands*, which were supported by far less structural and functional guidance.

Finally, in case the Office is confusing the present legitimate "making by screening " claims with "reach through" claims, Applicants note that claims enabled by screening techniques (and here, alternately by rational design) cannot be rejected under section 112. The Office in its Trilateral Project 3b, entitled "Mutual Understanding in Search and Examination, Report on Comparative Study on Biotechnology Patent Practices, Theme: Reach Through Claims" found it important to distinguish between legitimate "making by screening" and "reach through" claims. Wands itself establishes that screening is a legitimate mode of making additional species of a claimed genus.

Because one of skill can readily practice desired species across the scope of the claims either using logical engineering based on structures provided, or by random mutation and screening of provided structures using provided techniques, Applicants respectfully request withdrawal of the rejections.

CONCLUSION

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the claims are deemed not to be in condition for allowance after consideration of this Response, a telephone interview with the Examiner is hereby requested. Please telephone the undersigned at (510) 769-3510 to schedule an interview.

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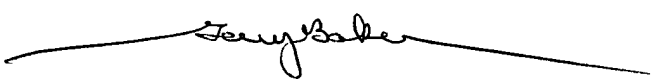
Respectfully submitted,



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Attachments:

1) A transmittal sheet;
2) Additional copies of submitted IDS references; and,
3) A receipt indication postcard.